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Prospective audit of exudative age-related macular degeneration: 12-month outcomes in treatment-naïve eyes

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Abstract: Purpose: To report the 12-month outcomes of 1,140 treatment-naïve eyes with exudative age-related macular degeneration (wet AMD) who were treated for 12 months with intravitreal anti-VEGF drugs in routine clinical practice. Methods: Index visit characteristics, such as lesion type and size, visual acuity (VA in logMAR [Logarithm of the Minimal Angle of Resolution] letters), as well as treatments, outcomes (VA, lesion activity status) and ocular adverse events were recorded in a prospectively designed electronic database. Index visit characteristics associated with the 12-month VA outcome were identified using mixed effects linear regression. Results: Mean change in VA in the cohort after 12 months was +4.7 logMAR letters (95%CI: 3.4 to 6.1) with a mean of 7.0 injections. No significant difference was found in change in VA or number of injections by type or size of the lesion. Median time to inactivation of lesions was 194 days. VA at the index visit was the strongest predictor for the 12-month outcomes. Infectious endophthalmitis occurred in 2 cases, retinal detachment in 1 case from a total of 9,162 injections. Conclusions: These findings indicate that VEGF inhibitors can achieve reasonably good outcomes for wet AMD when used in routine clinical practice.

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**Prospective Audit of Exudative Age-Related Macular Degeneration: 12-month
Outcomes in Treatment-Naïve eyes.**

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for the Fight Retinal Blindness! Project Investigators

Running head: 12-month outcomes of the FRB! Project wet AMD audit

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8

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19

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21

1 **ABSTRACT**

2 **Purpose**

3 To report the 12-month outcomes of 1,140 treatment-naïve eyes with exudative age-related
4 macular degeneration (wet AMD) who were treated for 12 months with intravitreal anti-
5 VEGF drugs in routine clinical practice.

6 **Methods**

7 Index visit characteristics, such as lesion type and size, visual acuity (VA in logMAR
8 [Logarithm of the Minimal Angle of Resolution] letters), as well as treatments, outcomes
9 (VA, lesion activity status) and ocular adverse events were recorded in a prospectively
10 designed electronic database. Index visit characteristics associated with the 12-month VA
11 outcome were identified using mixed effects linear regression.

12 **Results**

13 Mean change in VA in the cohort after 12 months was +4.7 logMAR letters (95%CI: 3.4 to
14 6.1) with a mean of 7.0 injections. No significant difference was found in change in VA or
15 number of injections by type or size of the lesion. Median time to inactivation of lesions was
16 194 days. VA at the index visit was the strongest predictor for the 12-month outcomes.
17 Infectious endophthalmitis occurred in 2 cases, retinal detachment in 1 case from a total of
18 9,162 injections.

19 **Conclusion**

20 These findings indicate that VEGF inhibitors can achieve reasonably good outcomes for wet
21 AMD when used in routine clinical practice.

22

23

1 While the efficacy of ranibizumab (Lucentis ®, Novartis, Switzerland), bevacizumab
2 (Avastin ®, Roche, Switzerland) and aflibercept (Eylea®, Bayer, Switzerland) for exudative
3 age-related macular degeneration (wet AMD)¹ has been convincingly demonstrated by tightly
4 controlled phase 3 clinical trials,²⁻⁷ it is still not certain that the results of these studies will be
5 replicated in the real world after the new drugs have been approved for general use. Many
6 patients being treated for wet AMD in the general community may not have met inclusion
7 criteria of the clinical trials. Even if they had, a heavy treatment burden on all involved in
8 routine retinal practice has led to dosing regimens that are less intensive than those used in
9 the pivotal trials, such as the *pro re nata* (PRN) and treat-and-extend regimens.^{8,9}
10
11 The Fight Retinal Blindness! (FRB) Project has established a prospective audit system that
12 can anonymously track outcomes of treatment of retinal disease, such as wet AMD, in large
13 numbers of patients treated in routine retinal treatment centres.¹⁰ Here we describe the 12-
14 month outcomes, including visual acuity, grading of lesion activity and adverse events, for
15 1,140 treatment-naïve participants in the FRB! Project wet AMD audit.

1 **METHODS**

2 **Study design & Setting**

3 This is an observational study utilising anonymised longitudinal data from the FRB registry
4 that were captured during routine clinical practice. All treatment decisions and visit schedules
5 were entirely at the discretion of the treating physician and patient. Details of the FRB project
6 data tracking system have been published.¹⁰ The research followed the tenets of the
7 declaration of Helsinki. Patients were given information regarding the project and given the
8 opportunity to opt out of the project. Each of the three academic core centres from the
9 Universities of Sydney, Melbourne and Western Australia obtained approval from their
10 respective Human Research Ethics Committees (HREC) to conduct the project as a quality
11 assurance activity. Overarching ethical approval for the other centres was obtained from the
12 Royal Australian and New Zealand College of Ophthalmologists' HREC.
13 Patient data recorded from 27 retinal specialists located across Australia from January 2006
14 until September 2012 were aggregated for analysis. The project began collecting data from
15 the core centres in Sydney, Melbourne and Perth then spread to non-academic retinal services
16 in the capital cities of most Australian states.

17

18 **Participants and Variables**

19 Few eligibility criteria were applied beyond treatment-naïve eyes commencing treatment for
20 wet AMD that had been diagnosed by their treating ophthalmologist with VA > 20 letters. All
21 eyes in the database that commenced treatment between Jan 2004 and Nov 2011 were
22 included in this analysis, so that all potentially had 12 months follow-up. At the index visit,
23 i.e. the visit at which treatment was commenced, the study participants' age, angiographic
24 lesion criteria such as lesion type and greatest linear dimension (GLD), visual acuity
25 (Logarithm of the Minimum Angle of Resolution – LogMAR, recorded as letters read),
26 choroidal neovascularization (CNV) status (active, inactive), along with treatment history and

1 treatment decisions (treated or not treated and name of drug used) were recorded.
2 Investigators were asked to enter whichever VA reading was best: uncorrected, corrected or
3 pinhole. The best VA achieved during each visit was used for analysis. The judgement of
4 “active” or “inactive” was left to the investigator’s discretion, thus reflecting real-world
5 practice. It was suggested that Users should grade lesions as active if there was intra- or sub-
6 retinal fluid, or any other feature, present that could be attributed to activity of the
7 neovascular lesion. Follow-up visits recorded subsequent VA, CNV status, all treatment
8 decisions and any ocular adverse events. Three subgroups of interest were pre-specified:
9 occult lesions (OC), minimally classic lesions (MC) and predominantly classic lesions (PC).

10

11 **Statistical methods**

12 For continuous variables means or medians and interquartile range (Q1, Q3) were computed.
13 Seventeen percent of patients contributed both eyes to the study database; when measuring
14 variation and performing statistical tests at the index visit, fellow eyes were randomly
15 removed to ensure any possible inter-eye correlation would not bias estimates. Formal
16 comparisons were made using the non-parametric Kolmogorov-Smirnoff (KS) test, which is
17 sensitive to any difference in the underlying distribution of two samples.

18

19 The outcomes analysis used data from all eyes that completed 12 months follow-up, while the
20 safety analysis set included all available data over 12 months. We also examined outcomes
21 for eyes that did not complete 12 months follow-up due to withdrawal from treatment or loss
22 to follow-up. Study endpoints included 12-month longitudinal VA, time from first intravitreal
23 injection to inactivation of CNV and change in CNV status over 12 months. Within-eye
24 changes in VA over 12 months were tested using the paired t-test. Longitudinal VA data were
25 plotted using a Lowess smoothed regression line.^{11,12} A mixed effects regression model was

1 fitted to the longitudinal VA data to examine the effects of lesion type, GLD and age on VA
2 at 12 months.
3
4 Kaplan-Meier analysis¹³ was used to examine time from first injection to inactivation of CNV
5 status. All observed adverse events were tabulated and reported. Analysis and plots were
6 done using R version 2.15.0.¹⁴
7
8
9

1 RESULTS

2 There were 1,140 eyes that completed 12 months follow-up (10,758 visits). The study
 3 population was 61% female and the mean age was 79.3 years (Q₁,Q₃: 75, 85). Mean visual
 4 acuity at the index visit was 57.1 letters (Q₁,Q₃: 45, 69) (Table 1). Owing to the quality
 5 assurance features of the FRB web-based data entry system, data quality was high for all
 6 variables (> 99.5% complete) with the exception of GLD (80% complete) and lesion type
 7 (88% complete).

8
 9 Table 1: Index visit characteristics of eyes that completed 12 months follow-up and those that
 10 did not

Characteristic	12-month Completers	Non-completers
Eyes	1,140	230
Visits	10,758	1,496
Median days follow-up (Q ₁ , Q ₃)	-	210 (111, 302)
Mean index VA (Q ₁ , Q ₃)	57.1 (45, 69)	52.5 (40, 65)
Mean age (Q ₁ , Q ₃)	79.3 (75, 85)	79.9 (75, 85)
Female	61.3%	58.3%
Median GLD (Q ₁ , Q ₃)	2,000 (1,300, 3,050)	2,315 (1,500, 3,390)
Lesion type		
Occult n (%)	529 (53.6 %)	109 (51.4 %)
Minimally classic n (%)	211 (21.4 %)	50 (23.6 %)
Predominantly classic n (%)	171 (17.3 %)	43 (20.3 %)
Other n (%)	76 (7.7 %)	10 (4.7 %)
Unclassified n	163	18

11 GLD: Greatest Linear Dimension; VA: LogMAR Visual Acuity

12

1 **Treatment administered**

2 A total of 8,013 injections were given to the 1,140 eyes that completed 12 months, a mean
3 (Q₁,Q₃) of 7.0 (5, 9) injections per eye (Table 2). The mean number of injections by lesion
4 type was similar. The majority of injections administered were ranibizumab (91%)
5 irrespective of lesion type, with the remainder being bevacizumab. For all lesion types the
6 interval between injections was greater when lesions were graded as inactive than when they
7 were graded as active.

8
9 Table 2: Injection frequency and type over 12 months follow-up

	Occult	Min class	Pred class	All
Mean (Q ₁ , Q ₃) number of				
injections	7.0 (5, 9)	6.8 (5, 9)	7.1 (5, 9)	7.0 (5, 9)
Median (Q ₁ , Q ₃) days				
between injections when				
active	35 (28, 52)	41 (29, 55)	35 (28, 56)	36 (28, 56)
Median (Q ₁ , Q ₃) days				
between injections when				
inactive	43 (35, 63)	49 (36, 63)	42 (33, 56)	42 (35, 63)
% Ranibizumab injections	91.3%	92.3%	91.4%	91.4%

10 Nin Class = minimally classic; predom = predominantly

11 **VA and GLD at the index visit**

12 There were notable differences in the distributions of VA and GLD among the lesion type
13 subgroups (Table 3, Figure 1). Visual acuity when starting treatment was lower for the PC
14 classic group than the OC subgroup (P<0.0001; KS-test) and the MC subgroup (P=0.01; KS-

test). GLD was lower in the PC group than either OC or MC: OC vs. PC (P=0.002); MC vs. PC (P=0.005); OC vs. MC (P=0.5), (Figure 1).

3

Table 3: Index visit visual acuity and greatest linear dimension with visual acuity change after 12 months

	Occult	Min class	Pred class	All
Mean (Q ₁ , Q ₃) VA Index visit	58.9 (50, 70)	57.1 (44, 67)	51.8 (37, 64)	57.1 (45, 69)
Mean 12 month VA change				
(95% CI*)	4.9 (2.1 to 7.1)	4.5 (1.9 to 7.1)	5.1 (1.9 to 8.2)	4.7 (3.4 to 6.1)
Median (Q ₁ , Q ₃) Index GLD	2,080 (1,255, 3,200)	2,015 (1,525, 3,030)	1,740 (1,065, 2,555)	2,000 (1,300, 3,050)

* Bias corrected and accelerated bootstrap 95 % confidence intervals¹⁵

7

Unadjusted 12 month VA outcomes

The mean within-eye change in visual acuity was a +4.7 letter improvement (95%CI: 3.4 to 6.1) for the study population as a whole. Similar clinically relevant mean improvements were observed for all subgroups (Figure 2A): OC +4.9 letters (95%CI: 2.1 to 7.1), MC +4.5 letters (95%CI: 1.9 to 7.1) and PC +5.1 letters (95%CI: 1.9 to 8.2). The Lowess lines indicate that all three groups exhibited a monotonic improvement throughout 12 months (Figure 2B).

14

Modelled 12 month VA outcomes

Given the observed imbalance at the index visit in VA and GLD for the 3 subgroups, a mixed effects regression model was fitted to the longitudinal VA measurements to mitigate potential confounding influences (Table 4). The model coefficients for the MC and PC lesions (relative to OC) of -1.3 and -0.5 respectively indicate that lesion subgroup had very little effect (less than 1.5 LogMAR letters) on visual acuity outcomes. The coefficient for Age of -0.03 indicated slightly worse outcomes with increasing age: a three decade increase in age was associated with a decreased gain of 1 LogMAR letter after 12 months of treatment. A 1mm

(1,000 μm) increase in GLD was associated with a reduced gain of 0.5 letters. The coefficient for Time indicated an annual mean improvement of 3.1 letters. Visual acuity at the index visit was a highly significant predictor of outcome.

Table 4: Coefficients from mixed effects model fit to 12-month longitudinal VA data.

	Model coefficient	t value
Index Visual Acuity	0.9	62.93
Index Visit Age	-0.03	-1.00
MC (relative to OC)	-1.3	-2.72
PC (relative to OC)	-0.5	-0.98
GLD 1000 μm	-0.5	-2.95
1 Year Follow-up	3.1	6.50

Lesion activity over 12 months

The median time from first intravitreal injection to lesions being graded as “inactive” was 194 days (95%CI: 174 to 216, Figure 3). Thirty seven percent of eyes were persistently graded as active during the 12 months of treatment. The median time between injections was 36 days (Q_1, Q_3 : 28, 56) while the lesions were graded as “active” and 42 days (Q_1, Q_3 : 35, 63) while graded “inactive”.

Eyes that did not complete 12 months follow-up

Two hundred and thirty eyes (17%) either withdrew from treatment or were lost to follow-up over the observed 12-month interval (non-completers). Median follow-up time for these eyes was 210 days (Q_1, Q_3 : 111, 302). At the index visit non-completers were similar to completers in most respects except for lower VA (mean 57.1 vs. 52.5; $P=0.0004$, KS-test). The outcomes for non-completers are shown in longitudinal profiles in Fig 4.

1

2 **Safety**

3 Ocular adverse events observed over 12 months follow-up are summarised in Table 5. The
 4 most common adverse event was patient-reported post-injection pain (45 instances). Two
 5 instances of infectious endophthalmitis were reported out of a total of 9,162 injections.

6

7 Table 5: Adverse Events

	Frequency	Injections per AE
Post injection pain reported	45	204
Haemorrhage reducing VA > 15	5	-
Retinal detachment	1	9162
Non-infectious endophthalmitis	2	4581
Infectious endophthalmitis	2	4581
RPE tear	12	764
Cataract extraction / other surgery	15	611

8 VA = Visual Acuity; RPE = Retinal Pigment Epithelium

9

1 **DISCUSSION**

2 This analysis of outcome data that were collected prospectively and continuously from
3 patients receiving treatment for exudative AMD has produced a number of observations on
4 the use and outcomes of intravitreal therapy in routine practice. Mean visual acuity of the
5 main cohort improved significantly by +4.7 logMAR letters over the first 12 months of
6 treatment with a mean of 7 injections. The mean visual acuity of predominantly classic
7 lesions improved slightly more than that of the minimally classic or occult groups, although
8 eyes with predominantly classic lesions had lower visual acuity at the index visit. Otherwise,
9 lesion type and size made little difference to the pattern of treatment outcomes, of which the
10 strongest predictor was visual acuity at the first treatment visit. The median time to first
11 grading of lesions as inactive was 194 days, with 37% still active at 12 months. Safety
12 findings were similar to previous reports. These findings indicate that VEGF inhibitors
13 achieve good outcomes for wet AMD when used in routine clinical practice.

14
15 Several other observational studies of intravitreal therapy for neovascular AMD have recently
16 been published. The Swedish Lucentis Quality Registry found a good improvement in visual
17 acuity after 3 injections of ranibizumab, but this subsequently dropped back to pre-treatment
18 levels.¹⁶ Patients in that study received a mean of only 4.8 injections over 12 months, fewer
19 than in the present study. Similar results were found by the WAVE study and an analysis of
20 the German reinjection scheme.^{17,18} These studies that recorded lower gains in mean visual
21 acuities also had a lower mean number of injections.

22
23 An improvement in mean visual acuity after the first 12 months of treatment that was more
24 similar to our results has been reported by two other observational studies. A gain of 3.2
25 LogMAR letters was found with a mean of 5.1 injections in the French Lumiere study of 551
26 patients.¹⁹ Menghini et al. reported a mean improvement of 5 letters with a mean of 4

1 injections in 204 eyes.²⁰

2
3 An overall mean improvement of 4.7 logMAR letters in the current report is still somewhat
4 less than was reported in phase 3 clinical trials of ranibizumab.^{2,3} However the improvements
5 in these studies were primarily measured against the change of vision in the control groups.
6 Verteporfin-treated eyes had lost a mean of 9.5 letters by 12 months in ANCHOR, while
7 sham-treated eyes had lost 10.4 letters in MARINA. Seen in this light, the increase in visual
8 acuity found in the present analysis of outcomes of treated eyes in routine practice is
9 reassuring. This was achieved with a mean of 7.0 injections, significantly more than was
10 given in previously reported observational studies,¹⁶⁻²⁰ out of potentially 13 that would be
11 given with a strict monthly regimen. This frequency is similar to that of the CATT study, in
12 which a mean of 6.9 injections were given to the ranibizumab PRN group and 7.7 to the
13 bevacizumab PRN group.⁵

14
15 Median time to grading the lesion as “inactive” was 194 days. Thirty seven percent of lesions
16 were consistently graded as active throughout the first year of the study. As might be
17 expected, these eyes received more injections. A related variable, presence of fluid at the 1-
18 year visit, was reported in 81% of bevacizumab PRN and 56% of ranibizumab monthly
19 groups of the CATT study.⁵ It appears that reasonably good visual acuity outcomes can be
20 obtained despite many eyes remaining active much or all of the time.

21
22 Lesion characteristics, particularly lesion size (GLD) and type, did not significantly affect the
23 outcomes of this study. Lesion type also had little effect on outcomes in retrospective
24 analyses of MARINA and ANCHOR, in which mixed lesions had similar outcomes to purely
25 classic or purely occult lesions.^{21,22} Menghini et al. also found no effect of lesion type on
26 visual outcome after 24 months treatment in another observational study.²⁰ In a recent report

1 from Comparison of AMD Treatment Trials, predominantly or minimally classic vs. occult
2 CNV was not included in the final multivariate model of change in VA at 1 year because it
3 was not statistically significant.²³ Predominantly or minimally classic lesions
4 were independently associated with less improvement in VA at 1 year in that study. Similarly,
5 another recent report found no difference in VA outcome for occult, minimally classic or
6 predominantly classic lesions in the PIER study.²⁴

7
8 The rate of serious adverse events was consistent with previous experience. Infectious
9 endophthalmitis occurred in 2 patients, an incidence of 2.2 per 10,000 injections. Non-
10 infectious endophthalmitis was reported in 2 more cases. Retinal detachment occurred in 1
11 eye, an incidence of 1.1 per 10,000 injections; this is similar to the rate at which retinal
12 detachments are reported to occur in the general population.²⁵ Mild adverse events appear to
13 be under-reported, since there were only 45 episodes of post-injection pain. This indicates
14 that registries may not accurately track outcomes that clinicians do not believe are clinically
15 significant.

16
17 This study, like all observational studies, has some limitations arising from the way in which
18 data were collected. Subjective criteria such as lesion activity or lesion type may not be
19 uniformly graded in observational studies since they are reported by the treating physicians
20 rather than a centralised Reading Centre. Thus these determinations may have lower internal
21 validity than in a phase 3 clinical trial, but perhaps they are still meaningful since this is how
22 these clinically important determinations are actually being made in the real world. The
23 measurement of LogMAR visual acuity, the main outcome, is reasonably objective. Also,
24 case selection and treatment regimens in observational studies may be very different to
25 clinical trials and among different ophthalmologists. Nevertheless, the data presented show

generally consistent outcomes of treatment regimens, which appeared to be similar across the different centres (data not shown).

There are a number of further analyses that can be performed on observational data that we present here. A study of the efficacy of different treatment intensities will need to take into account “treatment by time” interactions (a treatment in the first 3 months is likely to have a greater affect than a treatment in the last 3 months) and the possibility that the outcome of treatment drives treatment intensity, with eyes responding poorly receiving more treatments than these that respond well, rather than *vice versa*. A study of poor responders would need to include not just the proportion of patients who, for example, lose 15 letters, but also analysis of their baseline characteristics, how the loss evolved over time and whether the causes could be identified by a case by case analysis referring back to the clinic notes in a selected subgroup. Treatment patterns and their different efficacies can also be identified: a *pro re nata* regimen will be revealed when treatments are given only when the lesion is graded as active, while a treat and extend regiment will have most treatments given when the lesion is graded as inactive.

The significance of data from observational studies is that they provide an indication of what is happening in routine clinical practice, in contrast to results of phase 3 clinical trials, which may or may not be achievable in general. The results we present of intravitreal therapy for wet AMD are reasonably good, at least in the Australian centres that chose to participate. Further research is warranted to determine the functional implications of persistent activity and whether cohorts of patients receiving routine treatment do as well as those in phase 3 studies when they are more closely matched to participants in those studies.

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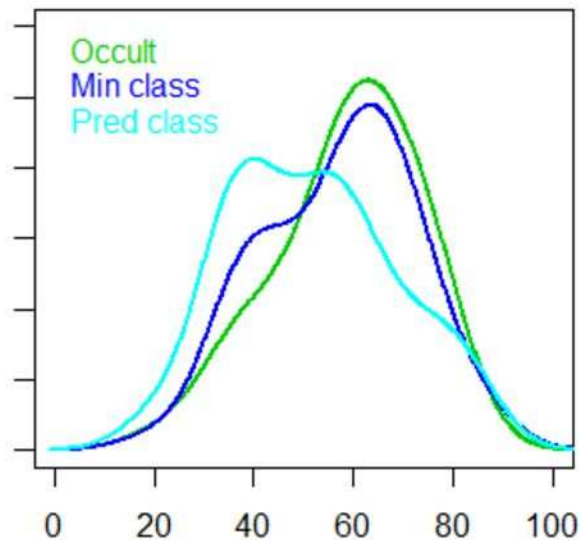
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REFERENCES

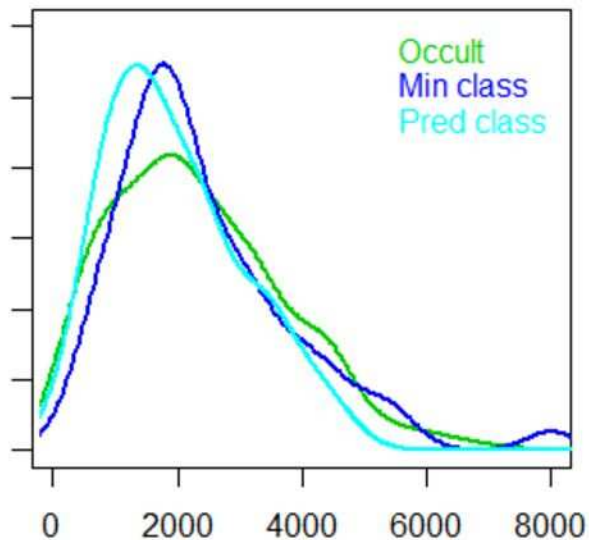
1. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A* 2002;99:11393-8.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-31.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-44.
4. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: Two-Year Results. *Ophthalmology* 2012;119:1388-98.
5. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897-908
6. Stewart MW. Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. *Br J Ophthalmol*. 2012;96:1157-8.
7. Traynor K. Aflibercept approved for macular degeneration. *American journal of health-system pharmacy*. *Am J Health Syst Pharm*. 2012;69:6
8. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*. 2009;148:43-58.e1.
9. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;117:2134-40.
10. Gillies MC, Walton R, Liong J, et al. Efficient capture of high quality data on outcomes of treatment for macular diseases: the Fight Retinal Blindness! Project. *Retina in press*

- 1 11. Cleveland WS. Robust Locally Weighted Regression and Smoothing Scatterplots. J Am
2 Stat Assoc 1979;74:829-36.
- 3 12. Cleveland WS. LOWESS: A Program for Smoothing Scatterplots by Robust Locally
4 Weighted Regression. Am Stat. 1981;35:54.
- 5 13. Kleinbaum DG, Klein M. Chapter 2: Kaplan-Meier Survival Curves and the Log-Rank
6 Test. In: Survival analysis: A self-learning text. USA: Springer, 2005:45-82.
- 7 14. R: A Language and Environment for Statistical Computing: Foundation for Statistical
8 Computing.
- 9 15. DiCiccio TJ, Efron B. Bootstrap confidence intervals (with Discussion). Statistical
10 Science 1996;11:189-228.
- 11 16. Hjelmqvist L, Lindberg C, Kanulf P, et al. One-year outcomes using ranibizumab for
12 neovascular age-related macular degeneration: results of a prospective and
13 retrospective observational multicentre study. J Ophthalmol. 2011;2011:405724.
- 14 17. Finger RP, Wiedemann P, Blumhagen F, et al. Treatment patterns, visual acuity and
15 quality-of-life outcomes of the WAVE study - A noninterventional study of
16 ranibizumab treatment for neovascular age-related macular degeneration in Germany.
17 Acta Ophthalmol. Published Online First: 22 November 2012. doi:10.1111/j.1755-
18 3768.2012.02493.x.
- 19 18. Heimes B, Lommatzsch A, Zeimer M, et al. Long-term visual course after anti-VEGF
20 therapy for exudative AMD in clinical practice evaluation of the German reinjection
21 scheme. Graefe's archive for clinical and experimental ophthalmology = Albrecht von
22 Graefes Arch Klin Exp Ophthalmol 2011;249:639-44.
- 23 19. Cohen SY, Mimoun G, Oubraham H, et al. Changes in visual acuity in patients with wet
24 age-related macular degeneration treated with intravitreal ranibizumab in daily
25 clinical practice. The Lumiere study. Retina Published Online First: 21 December
26 2012.

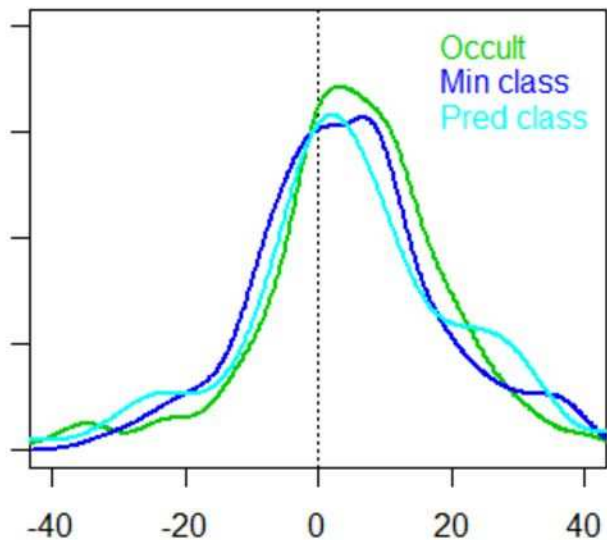
- 1 20. Menghini M, Kloeckener-Gruissem B, Fleischhauer J, et al. Impact of Loading Phase,
2 Initial Response and CFH Genotype on the Long-Term Outcome of Treatment for
3 Neovascular Age-Related Macular Degeneration. PLoS One 2012;7:e42014.
- 4 21. Boyer DS, Antoszyk AN, Awh CC, et al. Subgroup analysis of the MARINA study of
5 ranibizumab in neovascular age-related macular degeneration. Ophthalmology
6 2007;114:246-52.
- 7 22. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic
8 neovascular age-related macular degeneration: subgroup analysis of first-year
9 ANCHOR results. Am J Ophthalmol. 2007;144:850-57.
- 10 23. Ying GS, Huang J, Maguire MG, et al. Baseline Predictors for One-Year Visual
11 Outcomes with Ranibizumab or Bevacizumab for Neovascular Age-related Macular
12 Degeneration. Ophthalmology 2013;120:122-29.
- 13 24. Brown DM, Tuomi L, Shapiro H. Anatomical Measures as Predictors of Visual Outcomes
14 in Ranibizumab-Treated Eyes with Neovascular Age-Related Macular Degeneration.
15 Retina 2013;33:23-34.
- 16 25. Haimann MH, Burton TC, Brown CK. Epidemiology of retinal detachment. Arch
17 Ophthalmol. 1982;100:289-92.
- 18
- 19
- 20 Figure 1: Density plots of visual acuity (A) and greatest linear dimension (B) at the index
21 visit by lesion type.
- 22 Figure 2: Density plot of within group changes at 12 months (A) and fitted Lowess lines
23 showing subgroup changes in VA over 12 months (B)
- 24 Figure 3: Kaplan-Meier plot of time from active lesion first being graded as inactive.
- 25 Figure 4: Fitted Lowess lines showing changes in VA over 12 months for non-completers
26 (A,B,C) and completers (D).



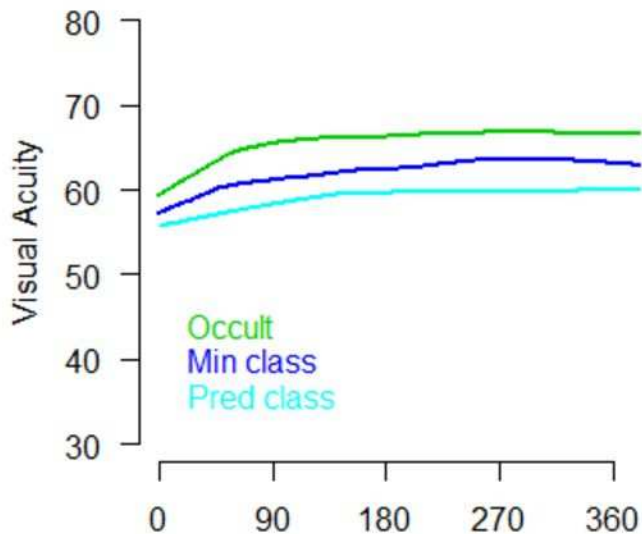
Index visual acuity (letters LogMAR)



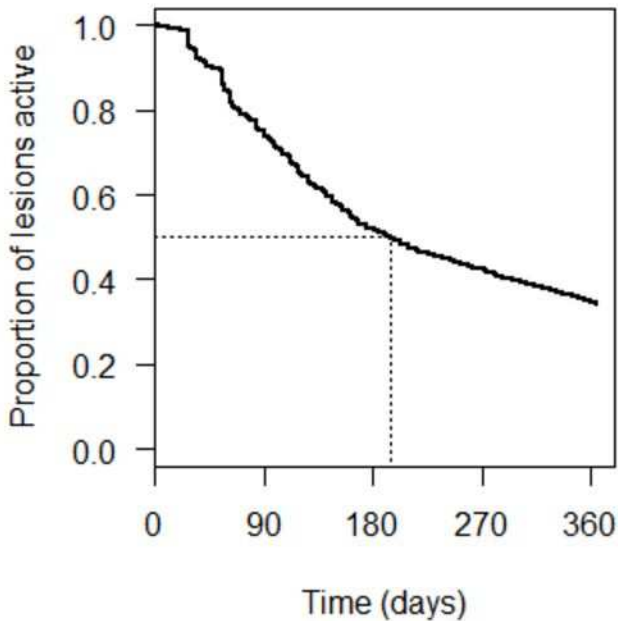
Greatest linear dimension (microns)

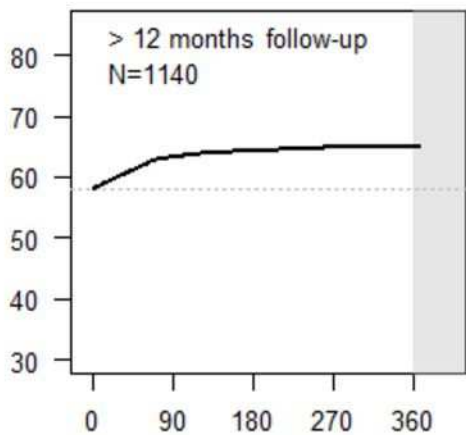
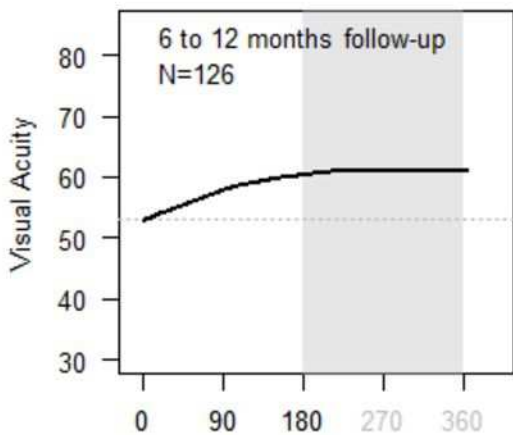
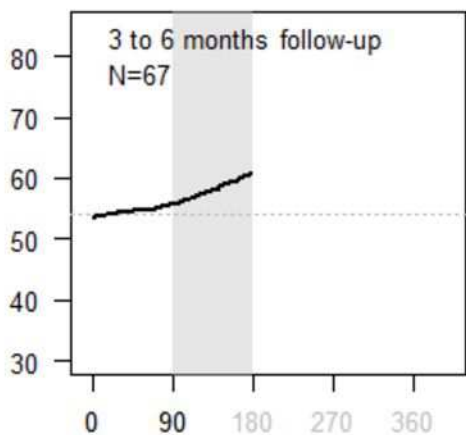
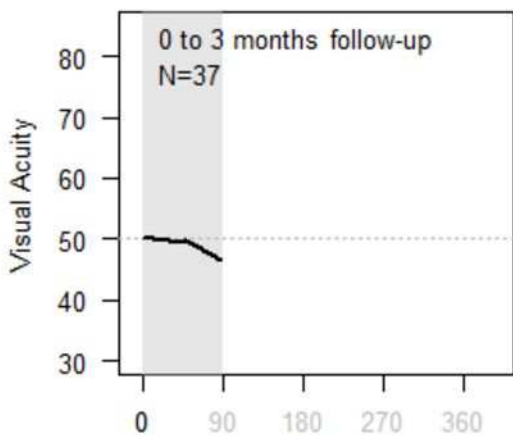


12 month change in visual acuity



Follow-up (days)





Follow-up (Days)

Follow-up (Days)